

| Notice of Allowability | Application No. | Applicant(s) | |
|-------------------------------|------------------|-----------------|--|
| | 10/628,432 | CORCORAN ET AL. | |
| | Examiner | Art Unit | |
| | William W. Moore | 1656 | |

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address--*

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. This communication is responsive to the Response of 17 October 2005 and the amendment filed 31 January 2006.
2. The allowed claim(s) is/are 1,6,8,9 and 21-30.
3. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All
 - b) Some*
 - c) None
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
 - (a) including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
 - 1) hereto or 2) to Paper No./Mail Date _____.
 - (b) including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. Notice of References Cited (PTO-892)
2. Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. Information Disclosure Statements (PTO-1449 or PTO/SB/08),
Paper No./Mail Date 2004316,20040416 & 2 Oct 2005.
4. Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. Notice of Informal Patent Application (PTO-152)
6. Interview Summary (PTO-413),
Paper No./Mail Date 20060202.
7. Examiner's Amendment/Comment
8. Examiner's Statement of Reasons for Allowance
9. Other _____.

EXAMINER'S AMENDMENT

Priority

Applicant's claim in the Declaration of Inventorship and at the first page of the specification filed 29 July 2003 to priority under 35 U.S.C. § 119 of the 29 July 2002 filing date of US provisional application No. 60/398,721, is hereby acknowledged. With respect to its E362Q modification disclosed at page 28 of the priority document, the elected invention of Group 9 enjoys the priority of the 29 July 2002 filing date of Applicant's provisional application, but the remainder of the structural characteristics of the invention of Group 9 have priority only to the 29 July 2003 filing date of the instant application. This is because the only ADAMTS4 truncation variant that comprises the E362Q modification disclosed in the parent provisional application has a structure extending beyond the disintegrin domain, where SEQ ID NO:32 terminates its ADAMTS structure, and throughout the thrombospondin region adjacent thereto, and comprising the FLAG peptide tag, i.e., the sequence represented by SEQ ID NO:31 herein, which is the invention of Group 8.

Information Disclosure Statement

Applicant's five Information Disclosure Statements [IDS] filed on 16 March, 15 April, and 18 May 2004, and on 5 July and 29 August 2005, are hereby acknowledged. In the last of these IDS, a reference citation is lined-through on the executed forms PTO-1449 that accompany this communication because the citation is redundant.

Election and Preliminary Amendment

Applicant's Amendment filed 31 January 2006 was requested by the Examiner in a telephonic interview on 30 January 2006 and is commemorated in the accompanying Examiner's Interview Summary. The amendment has been entered, canceling claims 2-5, 7, and the non-elected claims 10-20 and amending claims 1, 6, 8, and 9 to more

particularly describe embodiments of a modified human ADAMTS4 having structural features that correspond to those of the species elected by Applicant in the Response filed 17 October 2005, i.e., that comprise an inactivating amino acid substitution that replaces the zinc-coordinating glutamate in the metalloprotease domain with glutamine and that further comprise a disintegrin domain. The amendment adds claims 21-33 wherein several claims separately describe specific embodiments that were removed from claim 9 by the amendment and other claims drawn to other modifications disclosed in the specification. The Restriction Requirement is moot in view of these amendments.

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Cancel claims 31-33.

Amend claim 1 thus:

1. (Amended) An isolated, modified, human ADAMTS4 protein, ~~said modified ADAMTS4 protein~~ comprising
 - (a) an ADAMTS4 catalytic domain wherein the glutamate at the position corresponding to position 362 of SEQ ID NO:1 is substituted with a glutamine ~~a substitution of glutamine for glutamate at position 362~~, and
 - (b) a disintegrin domain.

Authorization for this examiner's amendment was given in a telephone interview with Mr. Brian Fairchild on 3 February 2006.

The following is an examiner's statement of reasons for allowance:

Applicant's Amendment presents claims to modified ADAMTS4 molecules that all require both the replacement of the glutamate at the zinc-coordination site of the ADAMTS4 metalloprotease catalytic domain with glutamine and the presence of an

intact disintegrin domain. The identifying structural and functional characteristics of a human ADAMTS4 molecule are defined at page 2, lines 25-27, and page 7, lines 10-24, of the specification and the prior art made of record herewith shows that the human ADAMTS4 metalloprotease-disintegrin is distinguishable from over a dozen other kinds of mammalian metalloprotease-disintegrin. While the prior art made of record herewith shows that it is routine to make inactivating substitutions of the glutamate at the zinc-coordination site of mammalian metalloprotease catalytic domains with other amino acids, including glutamine, in order to recombinantly express the metalloprotease catalytic together with its native, amino-proximal pre- and pro- domains in host cells that provide an endogenous protease that will cleave them from the catalytic domain. This is particularly the case where an artisan, such as Jepsen et al., made of record herewith wishes to form a crystal of a human metalloprotease for x-ray diffraction analysis. Yet the prior art teaches away from retaining a disintegrin domain together with a modified, inactivated, catalytic domain; indeed, all domains carboxy-proximal to an inactivated metalloprotease catalytic domain were heretofore eliminated in preparing human metalloproteases for recombinant expression in a host cell to use the catalytic domain to form a crystal.

Applicant instead incorporated the discovery that it was necessary to express both the ADAMTS4 catalytic domain and its adjacent disintegrin domain in order to provide a properly-folded, active, catalytic domain, indicating that the disintegrin domain, as well as inactivation of the catalytic domain would be required in order to form a crystal worthwhile for x-ray diffraction analysis. See lines 1-9 at page 37 of the specification. Only Souza et al., made of record herewith, disclose the crystallization of a mature metalloprotease comprising both a catalytic domain and a disintegrin domain but it was

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not prepared recombinantly and was instead purified from other components of venom glands of a viper, where the environment of the glands inhibits its catalytic activity.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.



NASHAATT NASHED PH.D.
PRIMARY EXAMINER

William W. Moore
3 February 2006